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Cluster headache is an autosomal dominantly inherited disorder in some families: a complex segregation analysis

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Abstract

We investigated the mode of inheritance of cluster headache in 370 familes. The probands were from a neurological clinic in Jutland and two departments of neurology in Copenhagen County, Denmark. The criteria of the International Headache Society were used. The patterns of segregation of cluster headache were assessed by complex segregation analysis performed with the computer program POINTER. Of the 370 probands with cluster headache, 25 had 36 relatives with cluster headache. The segregation analysis suggests that cluster headache has an autosomal dominant gene ($p<0.10$) with a penetrance of 0·30–0·34 in males and 0·17–0·21 in females. The gene is present in 3 to 4% of males and 7 to 10% of females with cluster headache. An autosomal dominant gene has a role in cluster headache in some families.

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Cluster headache is characterisited by recurrent, unilateral attacks of headache of great intensity and brief duration, accompanied by local signs and symptoms of autonomic dysfunction.[1] The attacks occur in series lasting weeks or months, so-called cluster periods. Cluster headache has not previously been considered to be an inherited disorder.[2 3] However, we have previously found a 14- and two-fold increased risk of cluster headache among first and second degree relatives of persons with cluster headache.[4] Another study found a 13-fold increase risk of cluster headache among first degree relatives.[5] This strongly suggests that the disease has a genetic cause.[6] Familial and non-familial cases of cluster headache have similar patterns of symptoms, but children have a statistically significant lower age at onset than their parents in the familial cases.[7] It is uncertain whether this is a real phenomenon or caused by memory bias.

The aim of the present study was to investigate the mode of inheritance with a complex segregation analysis,[8] in order to test different hypotheses of inheritance.

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Materials and methods

DATA COLLECTION

All living patients (probands) of Danish origin with a diagnosis of cluster headache according to the criteria of the International Headache Society (IHS)[1] were included. The probands were recruited from a neurological clinic (342 patients) covering Århus and east central Jutland, a headache research unit in a university hospital (60 patients), and from a department of neurology (19 patients) both covering Copenhagen County. A detailed semistructured headache history was taken by neurologists or neurological residents trained in headache diagnoses. All probands had a physical and a neurological examination to exclude other medical or neurological disorders. The probands received a mailed questionnaire. If the first questionnaire evoked no response, a second was mailed. The questionnaire response rate was 88% (370/421). The probands were asked about the number and sex of their first and second degree relatives, the age of their first degree relatives, and if any of their relatives had ever experienced cluster headache. Probands with a positive family history were interviewed by telephone (MBR). Subsequently, all possibly affected relatives were interviewed by telephone. Only relatives fulfilling the cluster headache criteria of the IHS had the diagnosis. The probands and the closest family members were interviewed about possibly affected dead relatives. A diagnosis of cluster headache was accepted only if this second hand history confirmed the diagnosis according to the criteria of the IHS, with the exception of criteria C, which specifies that headache is associated with at least one of the following signs on the pain side: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, or eyelid oedema.

The project was approved by the Danish Ethics Committees.

STATISTICAL ANALYSES

The complex segregation analysis is based on the distribution of the disease in nuclear families (parents and their offspring). Each pedigree ascertained on the basis of the probands can contain one or more nuclear families. The 370 cluster headache probands belonged to 366 pedigrees, which were split into 691 nuclear families with 1915 children. Table 1 shows the different mating types among the parents.

The segregation analysis was based on a mixed model, which incorporates mendelian inheritance of a single major gene locus, non-mendelian polygenic inheritance, and transmissible or non-transmissible environmental factors. The model assumes that the liability

Table 1 Distribution of the 691 cluster headache nuclear families by ascertainment and mating type, normal (N) and affected (A).

	Mating type	
Type of selection	*N×N*	*N×A*
Complete	—	317
Incomplete	358	16

Table 2 Sex and age specific frequency of cluster headache per 100 000 inhabitants

Age (y)	*Males*	*Females*
<20	26	8
20–39	109	24
40–59	153	40
⩾60	160	43

to the disease can be described by an underlying continuous liability scale (y). The liability of each person is assumed to be determined by the independent contribution of a major locus (g) (a locus that causes a displacement of more than one phenotypic standard deviation between normal and abnormal genotypes on the liability scale); a multifactorial component (c), attributable in theory to a large number of genetic or environmental influences, or both, acting additively and transmitted from parents to their children; and a random, non-transmitted environmental factor (e). The individual liability to disease in this model is then $y = g+c+e$. The variance (V) of y is similiarly divided into three components: $V = G+C+E$, where G, C, and E are the variances of g, c, and e respectively. The relative contribution of multifactorial transmission is defined by H, the heritability (in the narrow sense), which reflects genetic transmission not ascribed to a major gene and cultural transmission: $H = C/V$. If Z is a parameter that takes intergenerational differences in heritability into account then HZ denotes the parental heritability.

The major locus, which is assumed to have two alleles, A and A' producing three genotypes AA, AA', A'A', is defined by three parameters: q, the frequency of the major gene A'; t, the displacement, that is, the distance measured in standard deviations on the liability scale between the two homozygous genotype class means: and d, the degree of dominance, expressed as the position of the heterozygous class mean in relation to the homozygous class mean ($d = 0$ corresponds to a recessive gene, $d = 1$ to a dominant gene, and $d = 0.5$ to an additive gene).

The affected state is defined by a threshold (T) on the liability scale, which is determined from the risk of disease. The risk of cluster headache varies with sex and age. Each person was therefore assigned to one of eight different liability classes (table 2). Further details of the analysis are given in the appendix.

Results

The complex segregation analysis of cluster headache (table 3) gave the sporadic model (no family resemblance $H = q = 0$) a poor fit compared with the multifactorial model ($H>0$, $\chi^2 = 81{\cdot}25$, $df = 1$, $p<0{\cdot}001$). There was no evidence of an intergenerational difference ($Z = 1{\cdot}7$) for multifactorial inheritance ($\chi^2 = 0.69$, $df = 1$, $p>0{\cdot}70$). Among the three models that incorporated a major locus ($q>0$) the recessive model ($d = 0$) did not explain the observed segregation pattern as well as the additive ($d = 0.5$) and dominant ($d = 1$) models. The additive and dominant models were equally likely ($\chi = 6{\cdot}24$, $df = 3$, $p<0{\cdot}10$, and $\chi^2 = 6{\cdot}23$, $df = 3$, $p<0{\cdot}10$) with corresponding estimated parameters (same q and t of the dominant model equals $t \times d$ of the additive model). This was caused by the low frequency of the susceptibility allele (7×10^{-5}) and the resulting low probability that any of the affected patients were homozygous. In fact, no families had both parents affected (table 1). The likelihood surface was mapped using different starting values, but H always went to zero iterating all parameters in the general model.

The characteristics of the major dominant locus for cluster headache by liability class is shown in table 4. The penetrance (probability for disease given the genotype, P(disease | gentoype)) was almost the same in the males (liability classes 1–4), being 0·34 in the heterozygote or homozygote for the highest incidence group. The penetrance in females (liability classes 5–8) was slightly lower than found in males, being 0·21 in the heterozygote or homozygote for the highest incidence group. This means that after the age of 40 years, male heterozygote or homozygote carriers have a 34% risk and female heterozygote or homozygote carriers have a 21% risk of cluster headache. The gene is responsible for the disease in only a minority of those with cluster headache

Table 3 Results of complex segregation analysis for cluster headache

Model	*Heritability (H)*	*Z*	*Gene frequency (q)*	*Displacement between two homozygous means (t)*	*Degree of dominance (d)*	*$-2 \times lnL + K$*
Sporadic	0*	—	0*	—	—	−140·90
Multifactorial	0·61	1*	0*	—	—	−222·15
Multifactorial with generational difference	0·55	1·7	0*	—	—	−222·84
Recessive major locus	0*	1*	0·0183	2·85	0*	−217·05
Additive major locus	0*	1*	0·0000721	5·09	0·5*	−228.39
Dominant major locus	0*	1*	0·0000709	2·55	1*	−228.38

Z parameter that takes intergenerational differences in heritability into account, lnL natural logarithm of the likelihood, and K a constant. * Fixed parameters.

Table 4 Penetrance and contribution of the major dominant locus for each sex and age group of cluster headache

Sex	Age (y)	P(disease | genotype)	P(genotype | disease)	
		AA' or A'A'	AA	AA' or A'A'
Male	0–19	0·17	0·91	0·09
Male	20–39	0·30	0·96	0·04
Male	40–59	0·34	0·97	0·03
Male	60>	0·34	0·97	0·03
Female	0–19	0·10	0·82	0·18
Female	20–39	0·17	0·90	0·10
Female	40–59	0·21	0·93	0·07
Female	60>	0·21	0·93	0·07

(probability for genotype given disease, P(genotype | disease)). However, the gene is more often responsible for the disease in females than males, and more often in those below the age of 20.

Discussion

The increased familial risk of cluster headache strongly suggests that the disease has a genetic cause.[4,5] The complex segregation analysis with a pointer[8] supported the importance of a genetic factor, since the multifactorial model (H>0) gave a significantly better fit than the sporadic model (H=0). The segregation analysis suggested that an autosomal dominant gene is present in a minority of those with cluster headache. This was not statistically significant with a 5% level of significance ($p<0·10$), but it was the model which gave the best fit. The results indicate that the gene is twice as frequent in females with cluster headache as in males. The penetrance was estimated to be approximately 1·5-fold higher among males than females. This can only explain a fraction of the overall male preponderance of cluster headache. We did not use transmission probabilities (τ_2) in the analysis, since it has been shown not to be correctly implemented in POINTER.[9]

We conclude that cluster headache is at least partly the result of an autosomal dominant gene with a penetrance of 0·30–0·34 in males and 0·17–0·21 in females. The gene is present in 3–4% of males and 7–10% of females with cluster headache. Future research should be directed toward identification of the cluster headache gene by linkage analysis in order to confirm the above result.

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Appendix

Complex segregation analysis was performed with the computer program POINTER.[8] Nuclear families were distinguished according to whether or not they were ascertained through a pointer, which is defined as an affected patient who leads to the ascertainment of a nuclear family but who is not a member of this family.

There were 317 nuclear families ascertained through a parent affected by cluster headache, which provide complete selection of the possible phenotypes among the offspring (table 1). The remaining families were ascertained through children or other relatives, resulting in incomplete selection of the possible offspring phenotypes. Incomplete selection is corrected for in the analysis by taking into account the ascertainment probability (π) which is defined as the probability that an affected person is a proband. It may be estimated from the proportion of probands among affected sibs of each proband ($\pi = \Sigma\, a(a-1)/\Sigma\, a(r-1)$, where a is the number of independently ascertained probands and r the total number of affected sibs within the sibships). π was estimated at 0·24 for cluster headache families (seven probands belonged to three families).

All the parameters of the model were estimated by maximising the overall likelihood. To test the hypotheses, the relevant parameters were held constant while estimating the remaining parameters. The value reported was $-2\ln L + K$, where $\ln L$ is the natural logarithm of the likelihood and K is a constant. The difference between the values of $-2\ln L + K$ under the general model (with m parameters) and under a reduced model (with k parameters) is asymptotically distributed as a χ^2 with m-k degrees of freedom.

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